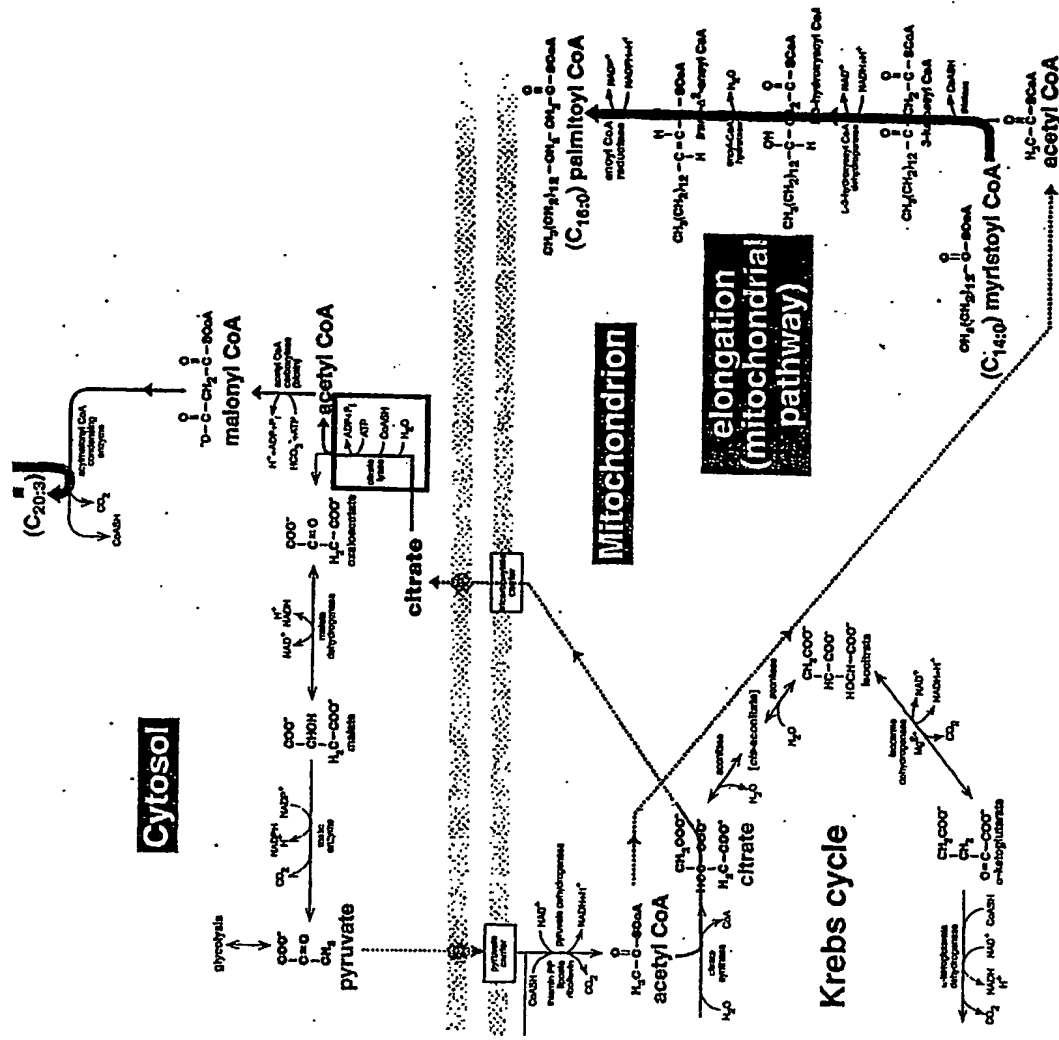


# ATP Citrate Lyase (ACL) catalyzes the production of cytosolic acetyl CoA



Adapted from: "Metabolism at a glance" (1999)  
J.G.Salway (Blackwell Science Ltd, England)

Figure 1

**ACL activity is downregulated in quiescent cells via  
a post-transcriptional mechanism**

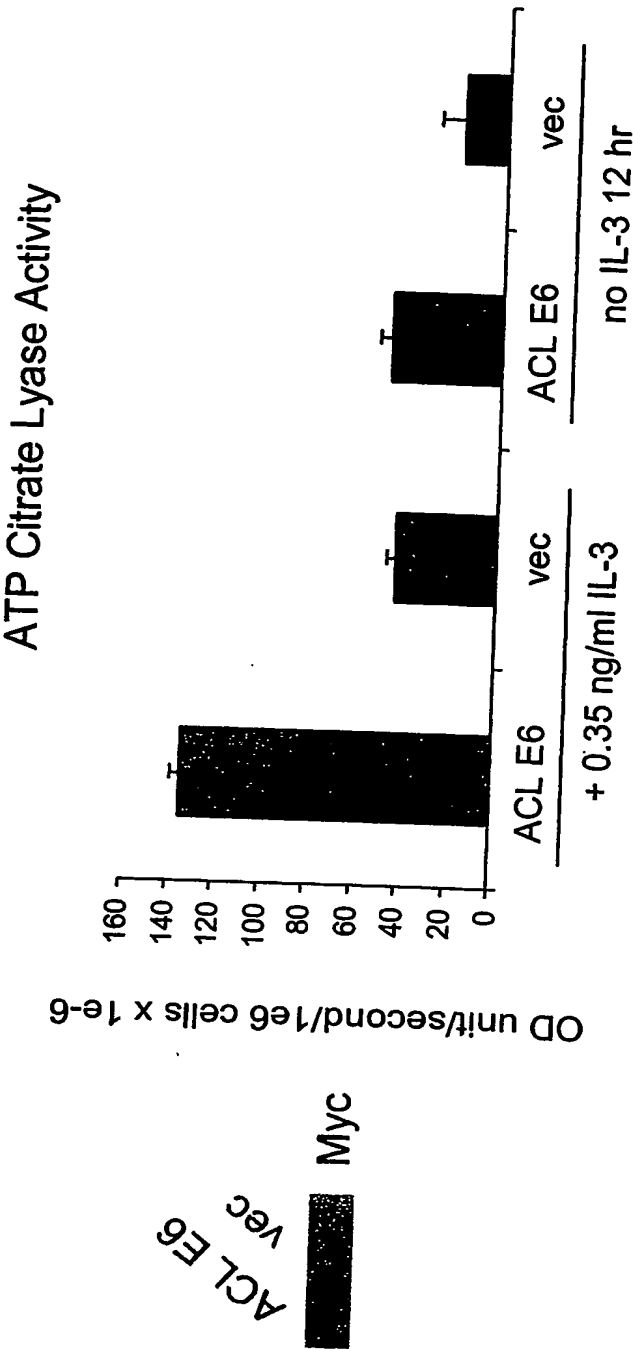


Figure 2

**(-)-Hydroxycitrate inhibits cell survival in a dose-dependent fashion at millimolar concentrations**

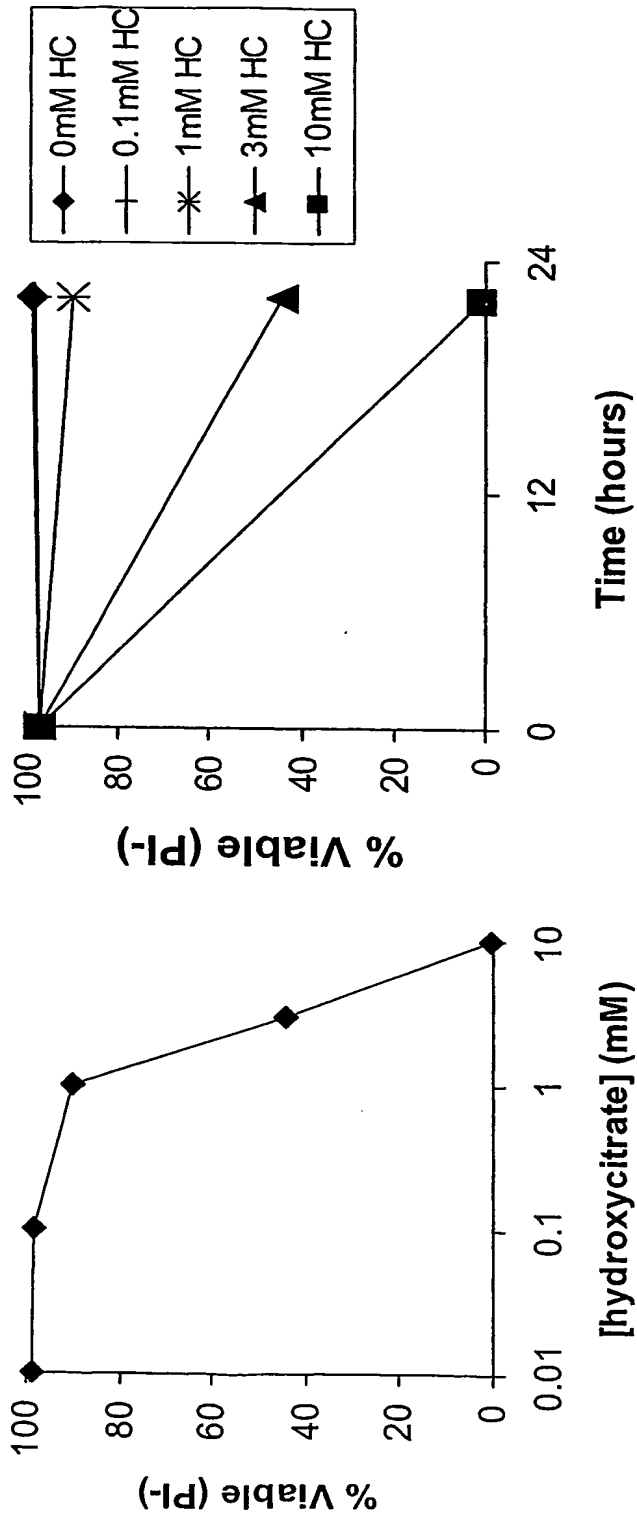


Figure 3

# Structure of a potent ACL inhibitor and its prodrug

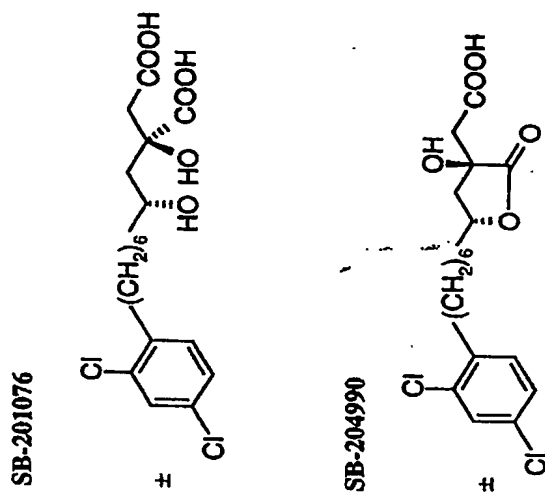


Figure 1 Structure of SB-201076 and its  $\gamma$ -lactone SB-204990

Figure 4

Pierce N.J., et al. (1998) The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Biochem J. 334, p113-119

# SB201076 inhibits ACL activity in a dose-dependent fashion

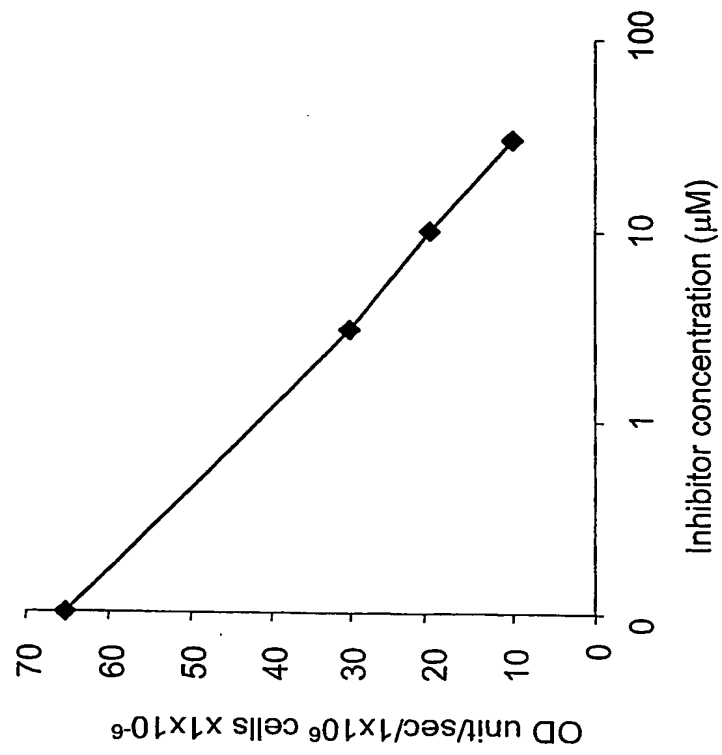


Figure 5

**SB204990 inhibits cell proliferation and survival  
in a dose-dependent fashion at micromolar concentrations**

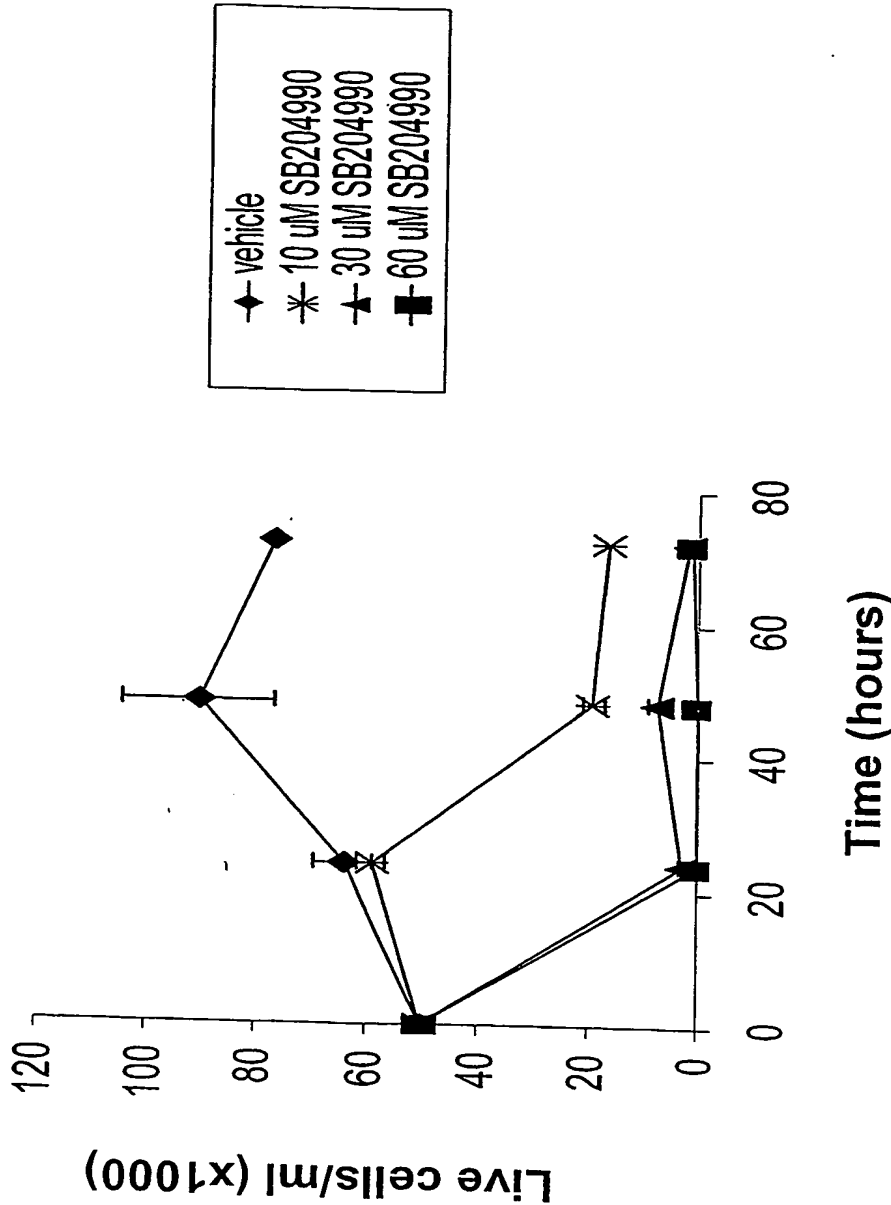
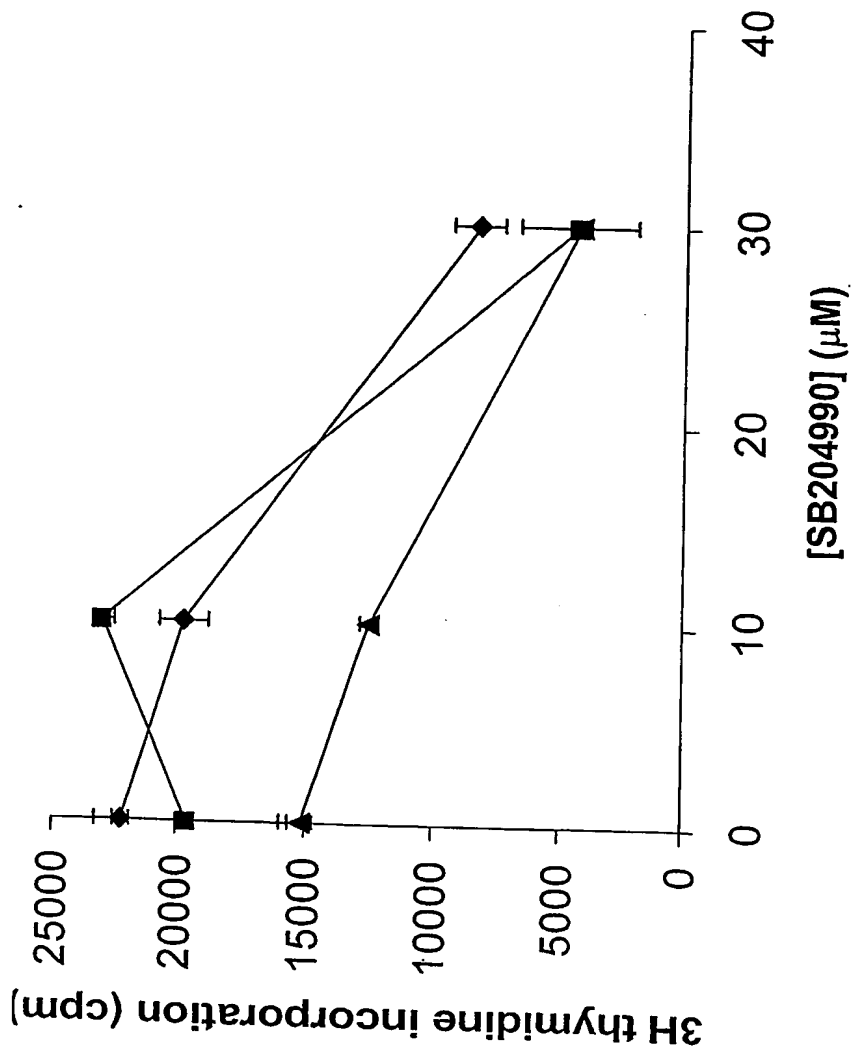


Figure 6

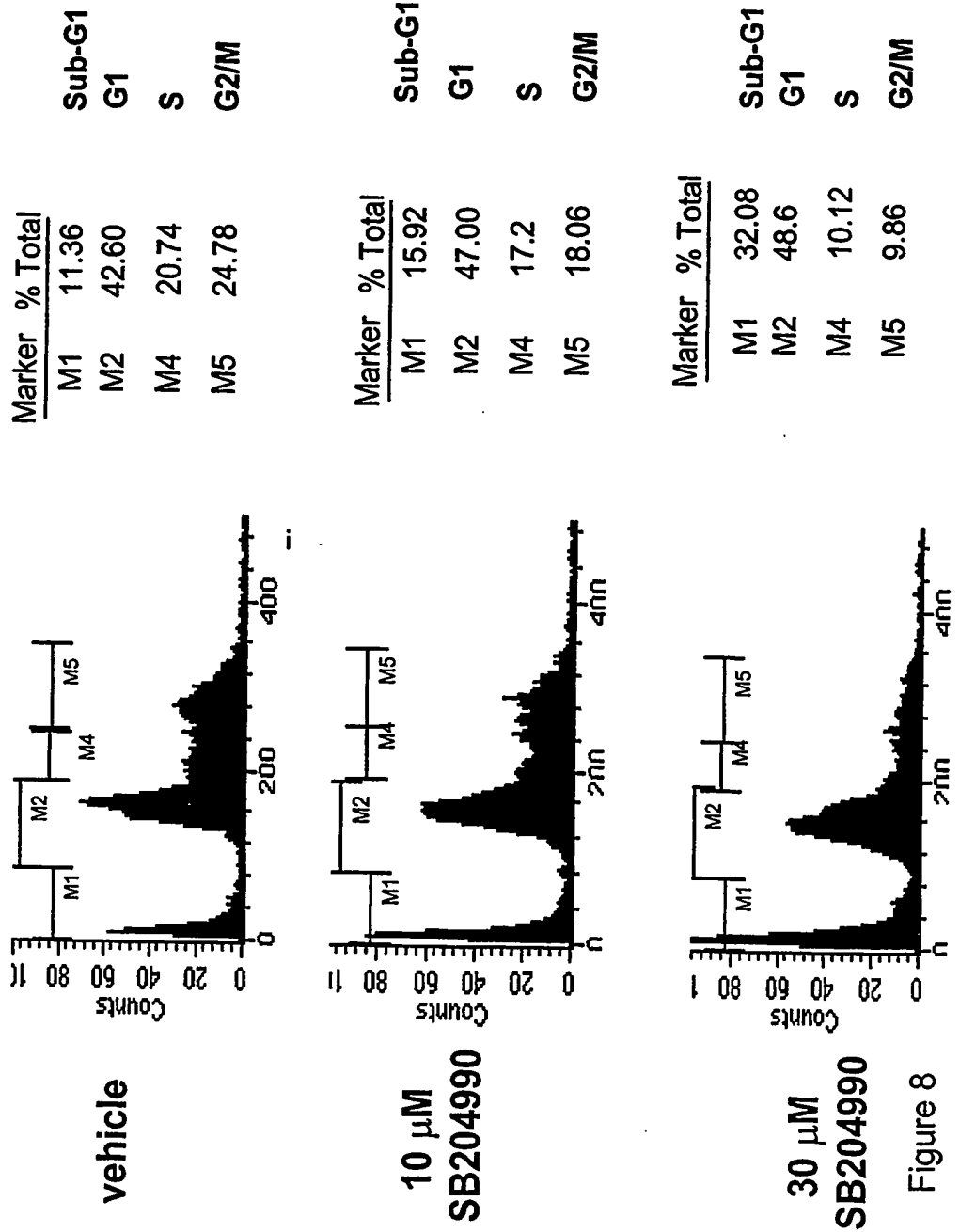
# ACL inhibition prevents the proliferation of immortalized hematopoietic cells in a dose-dependent fashion



(3 independent FL5.12 stable clones treated with the drug in the presence of IL3 for 20 hrs)

Figure 7

# ACL inhibition causes G1 arrest and apoptosis of proliferating cells





# ACL inhibition induces the surface expression of the apoptotic marker Annexin V in a dose-dependent fashion

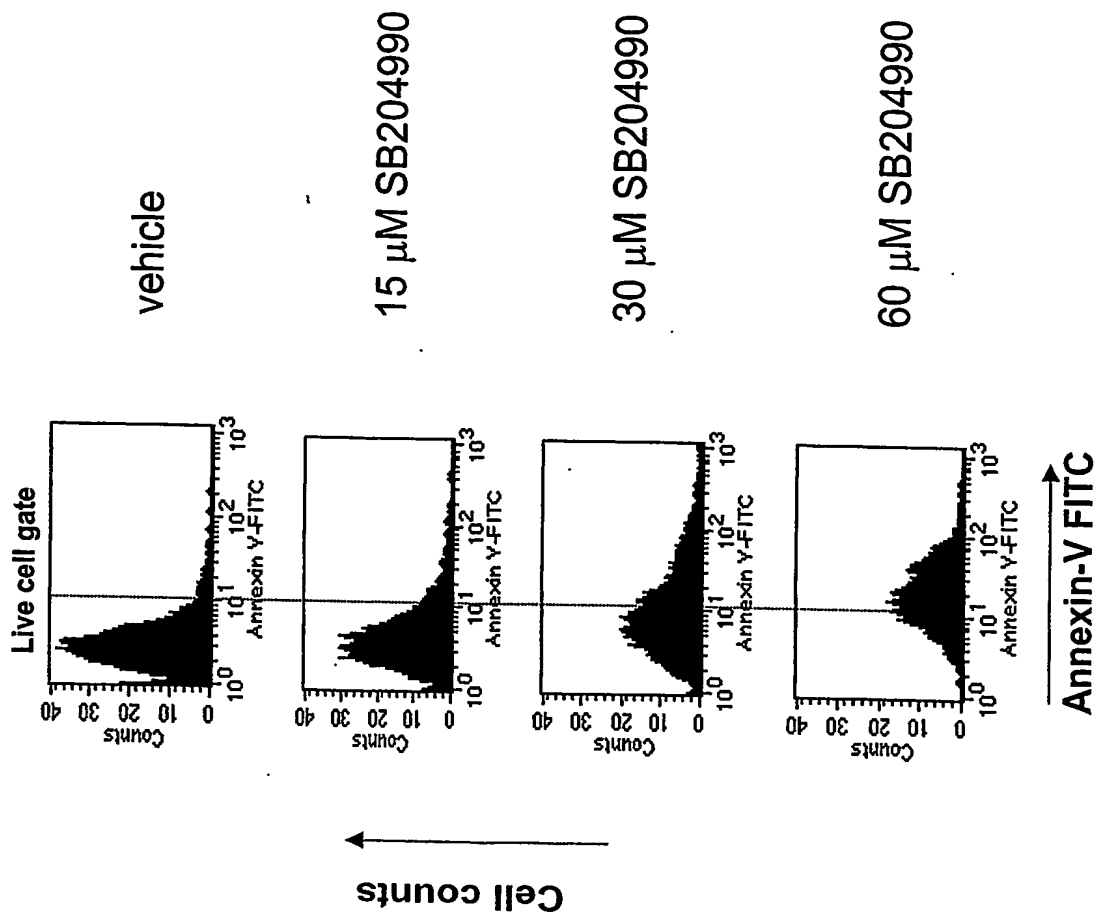


Figure 9

**Akt induces ACL activity independently  
of growth factor availability**

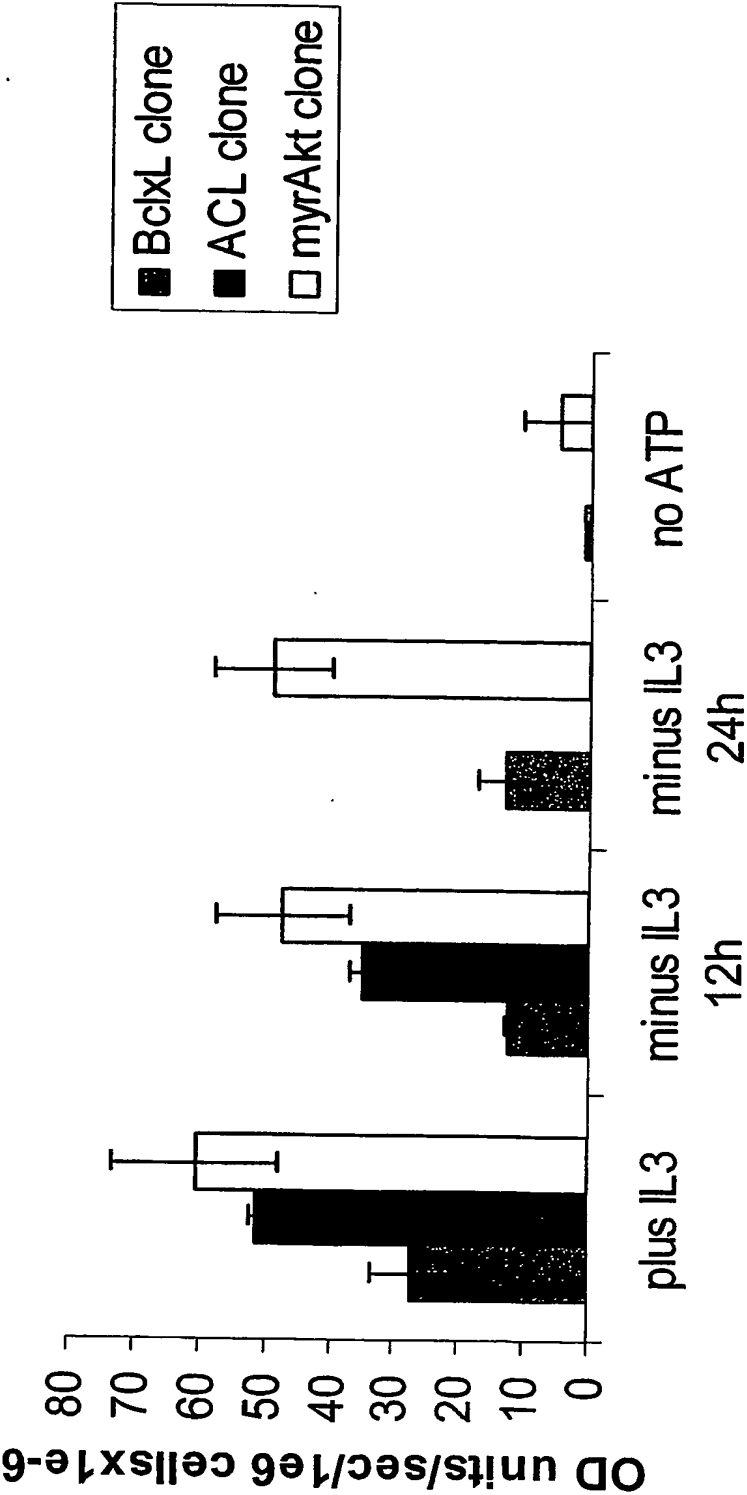


Figure 10

# ACL inhibition is selectively toxic to proliferating cells and to cells expressing active Akt

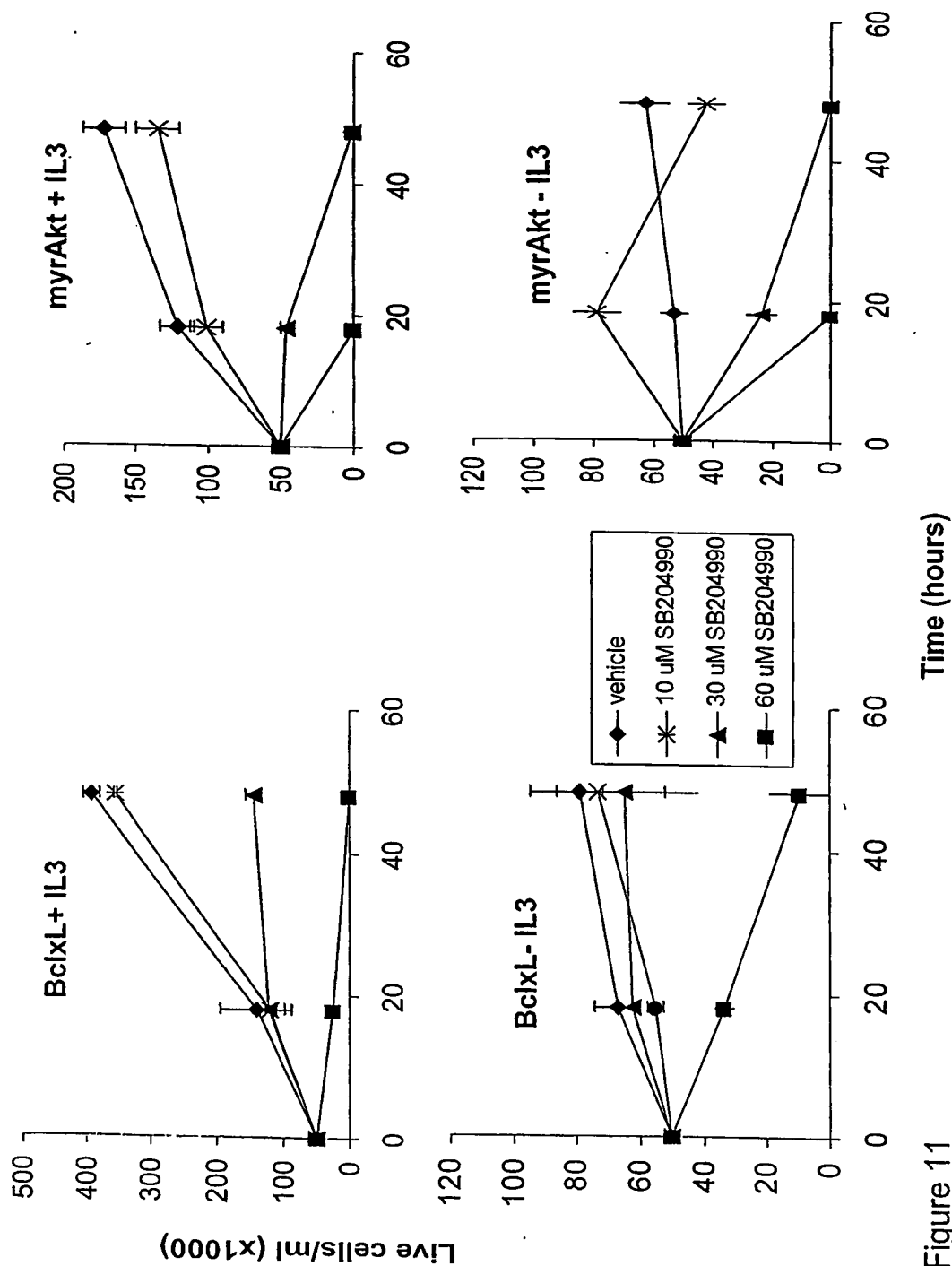


Figure 11

# Glioblastoma cell lines' response to ACL inhibition correlates with their activated Akt status

A

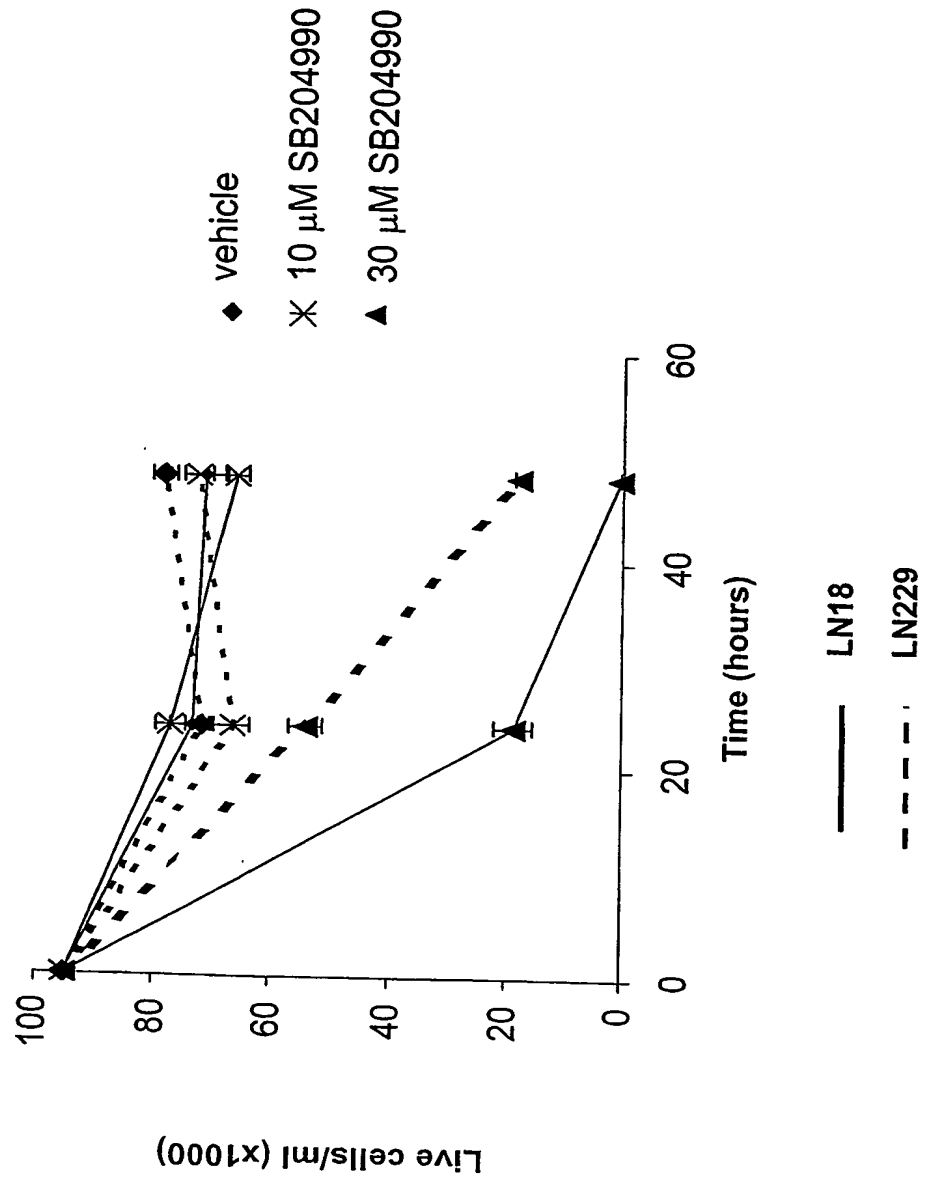


Figure 12A

**Glioblastoma cell lines' response to ACL inhibition  
correlates with their activated Akt status**

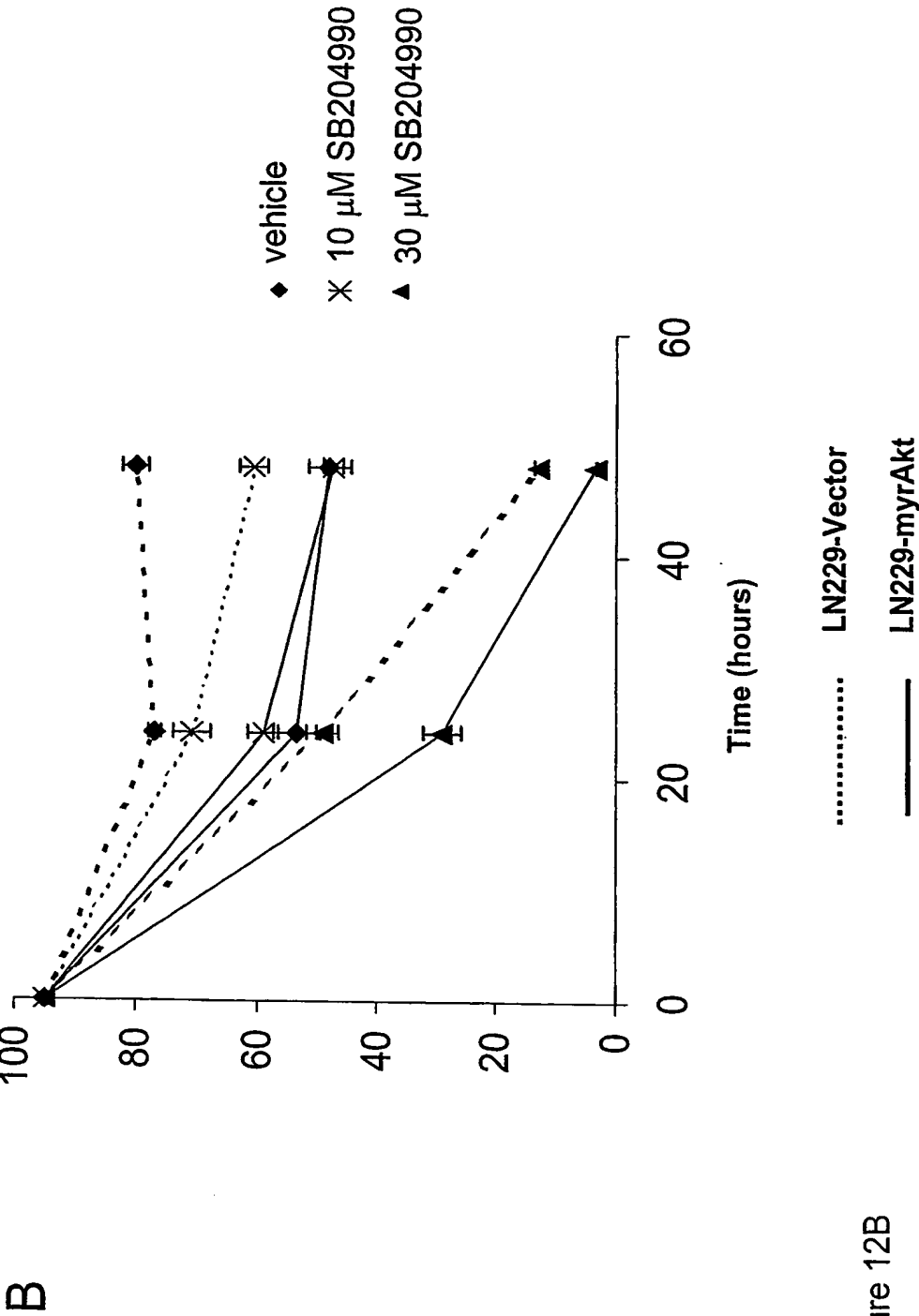


Figure 12B

# Proliferating cells are more sensitive to ACL inhibition-induced apoptosis

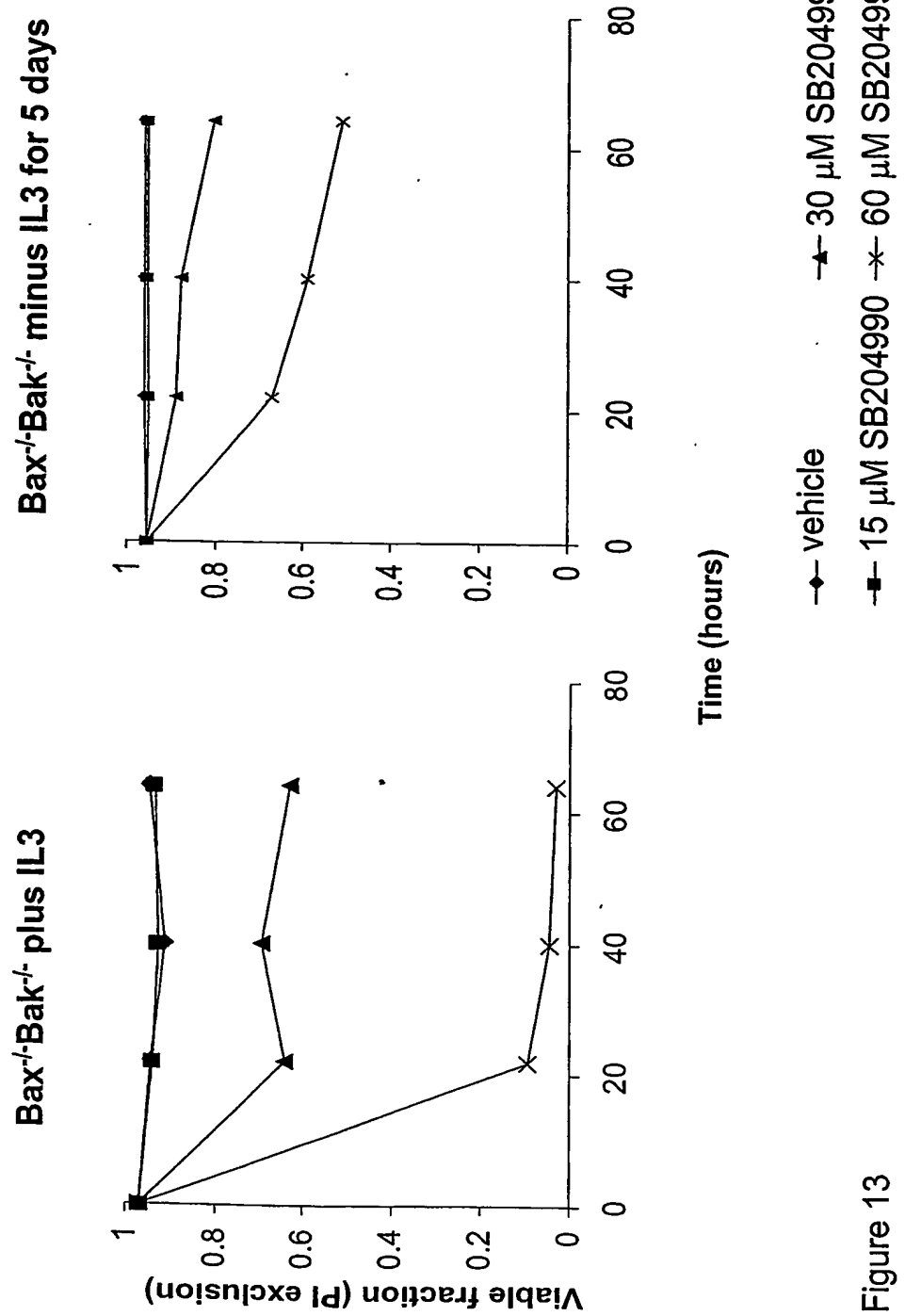


Figure 13

# ACL inhibition prevents growth factor-induced cell growth and cell cycle entry

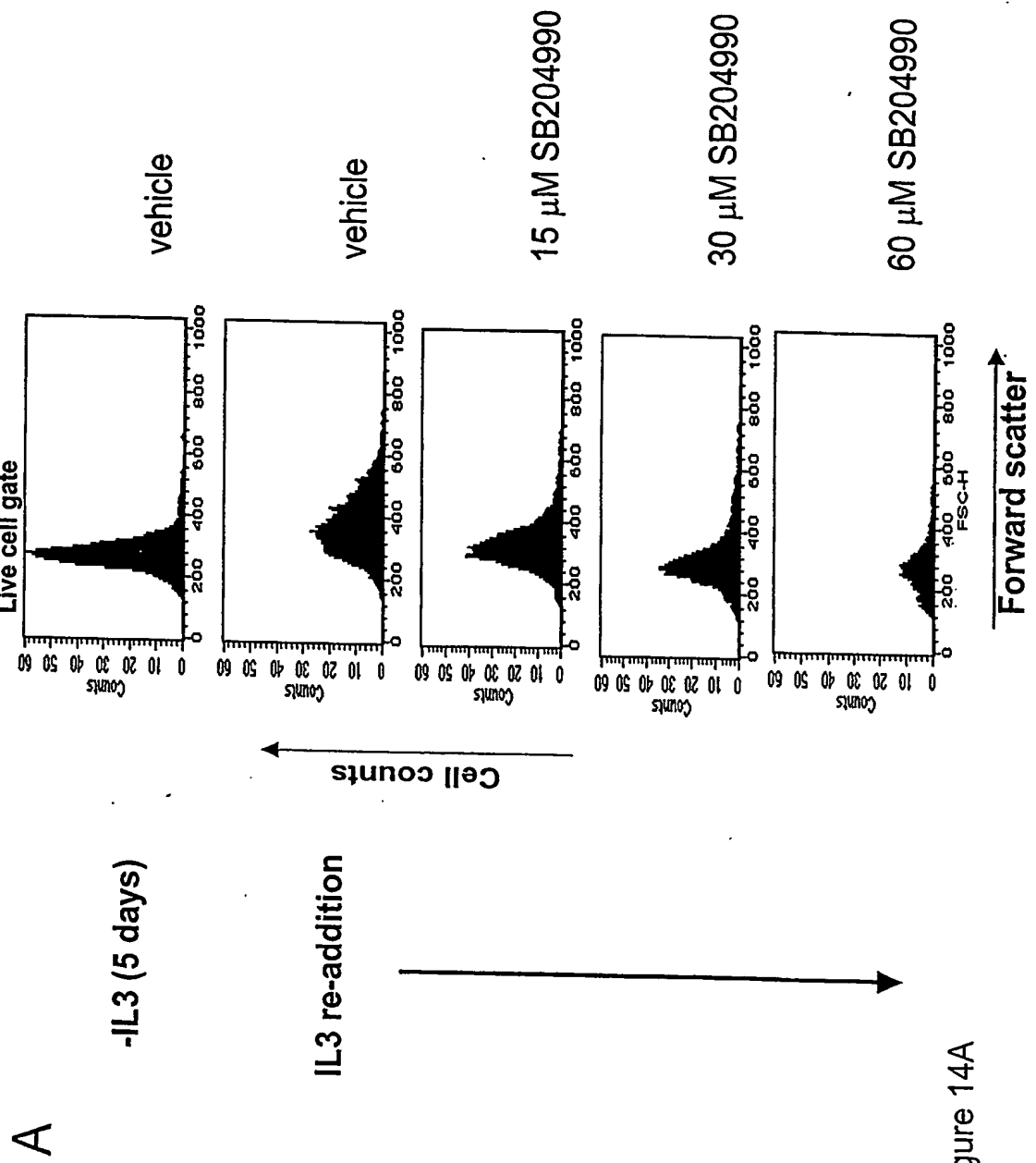


Figure 14A

ACL inhibition prevents growth factor-induced  
cell growth and cell cycle entry

B

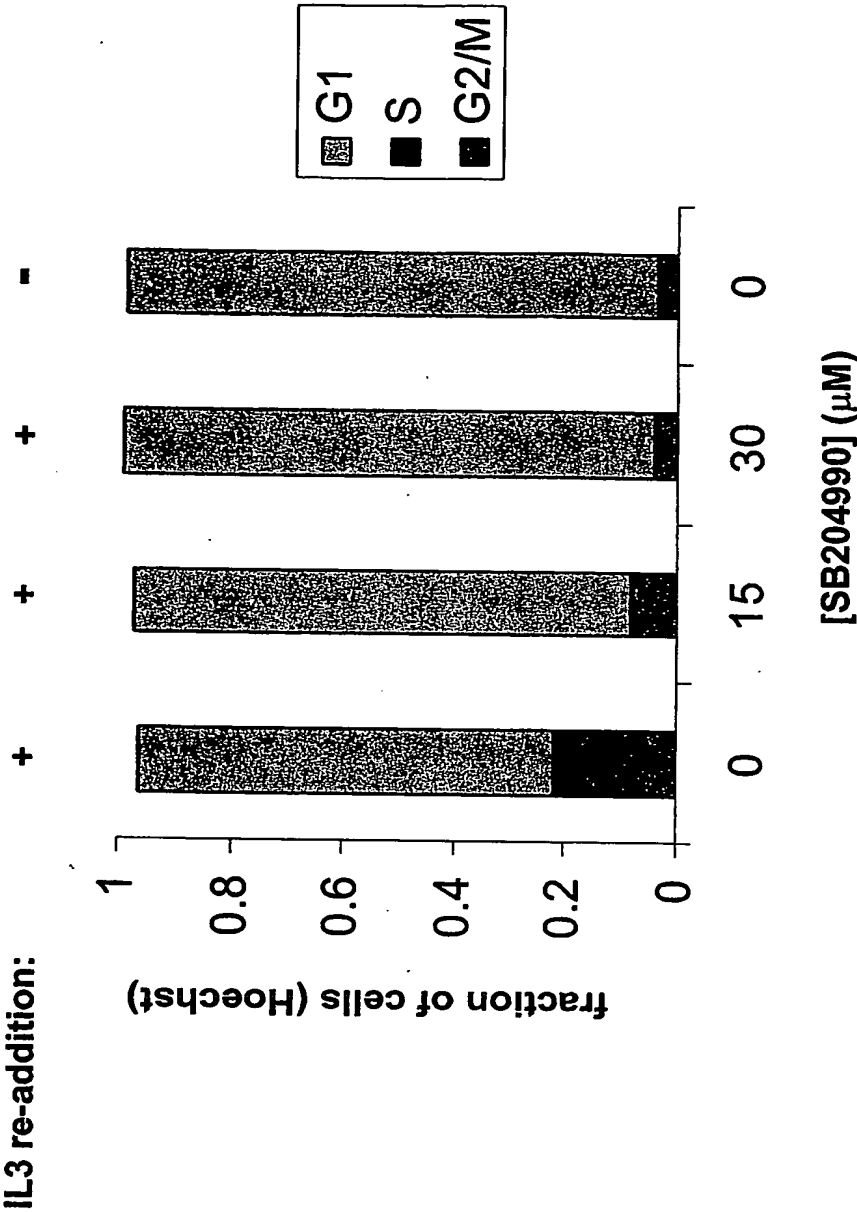
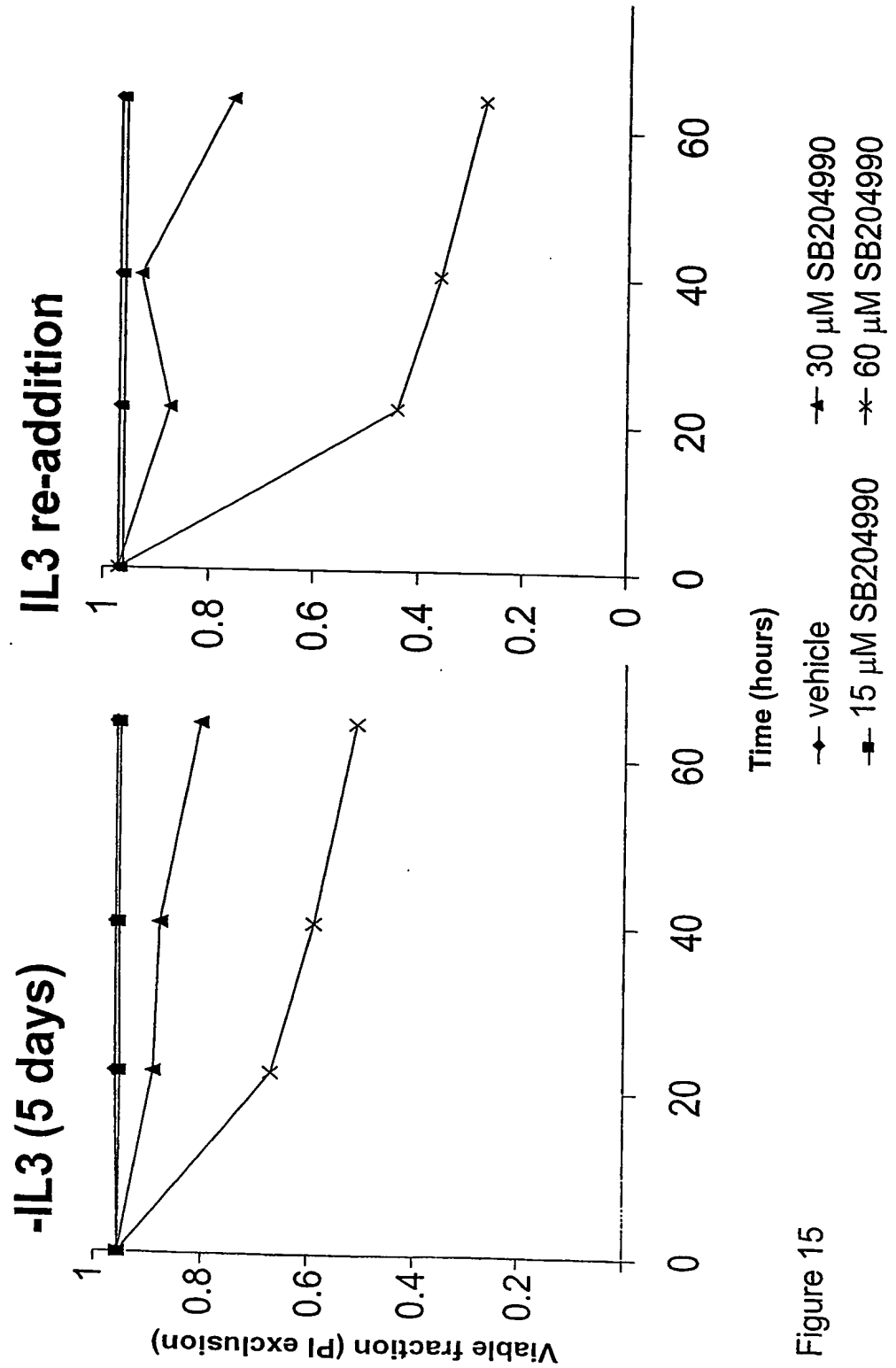


Figure 14B



# Mitogenic stimulation makes quiescent cells more sensitive to ACL inhibition-induced death



**ACL inhibition of cells expressing active Akt decreases  
their glycolytic rate**

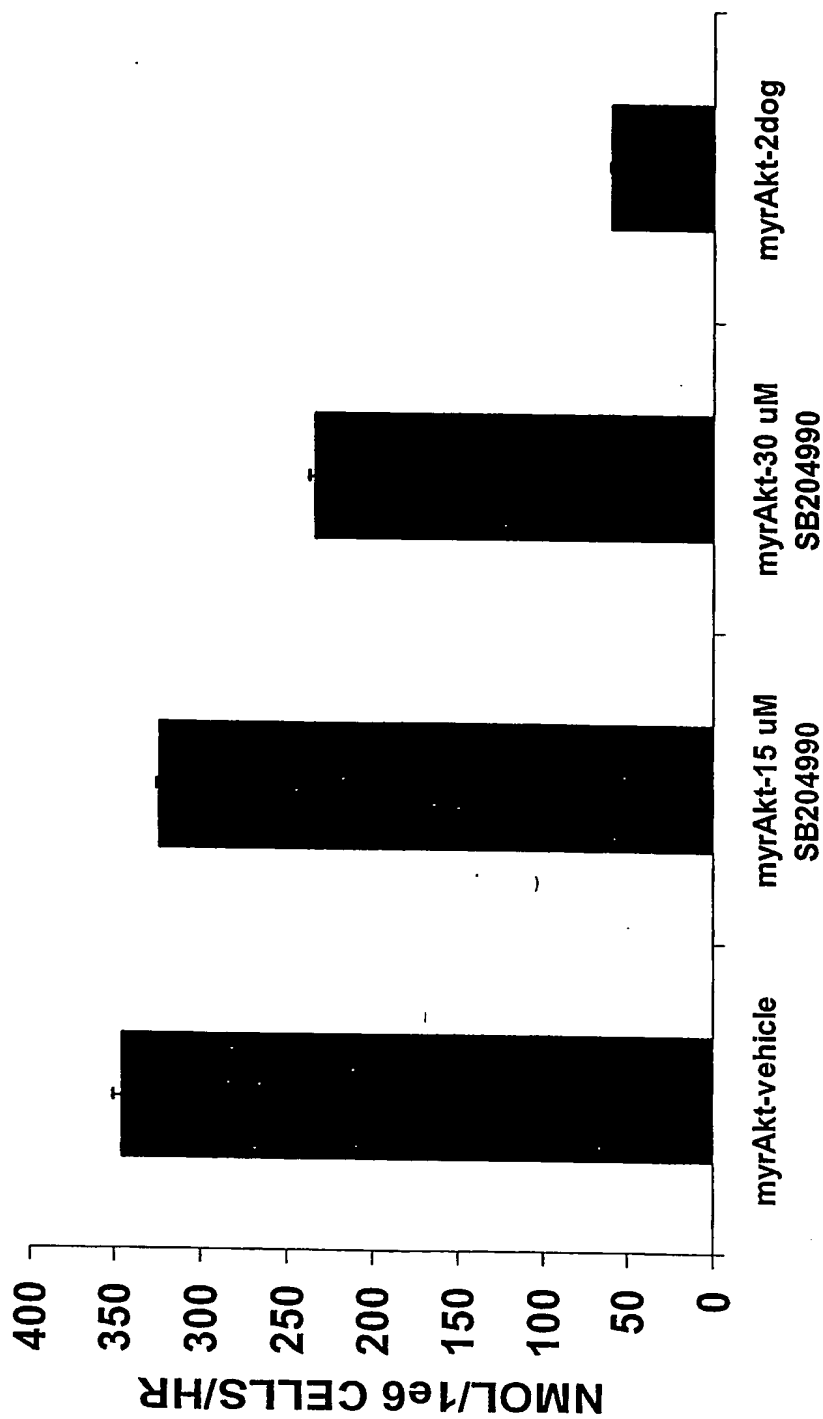
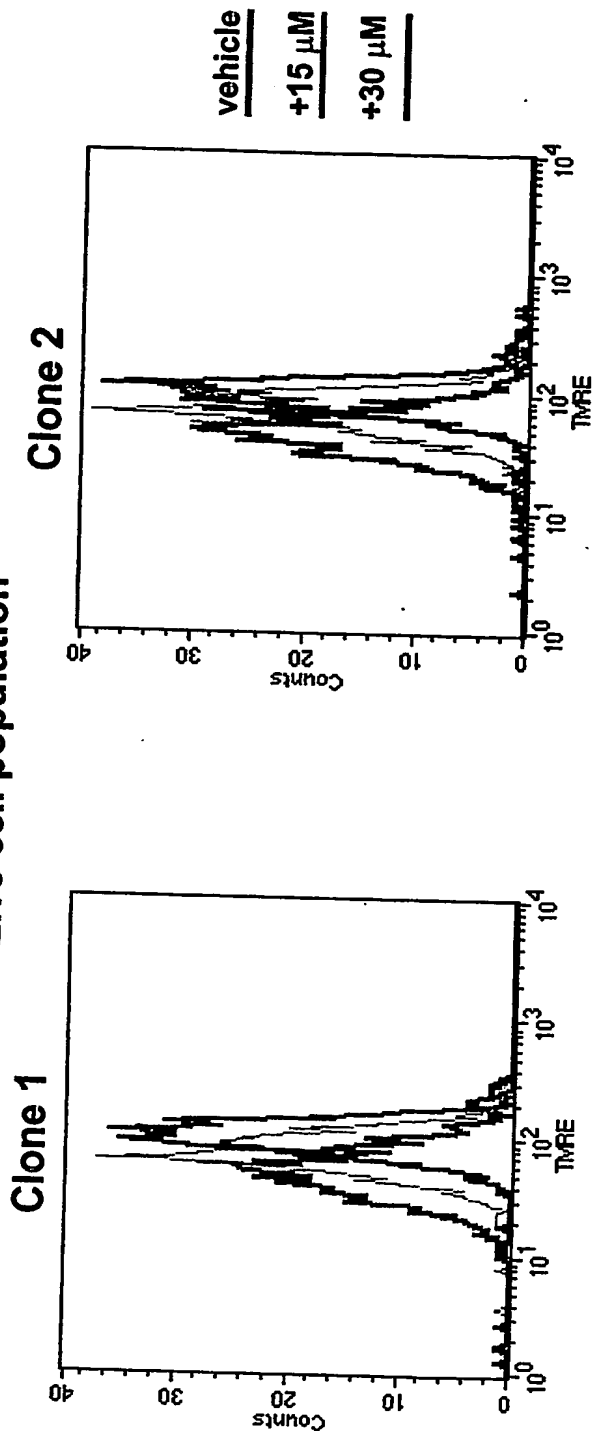


Figure 16

# Mitochondrial hyperpolarization upon ACL inhibition is dose-dependent

Live cell population



TMRE Mean Fluorescence Intensity

vehicle  
53.66

+15 μM SB204990  
76.41

+30 μM SB204990  
100.41

vehicle  
47.88

+15 μM SB204990  
73.12

+30 μM SB204990  
95.23

Figure 17

# ACL inhibition induced mitochondrial hyperpolarization precedes annexin V positivity

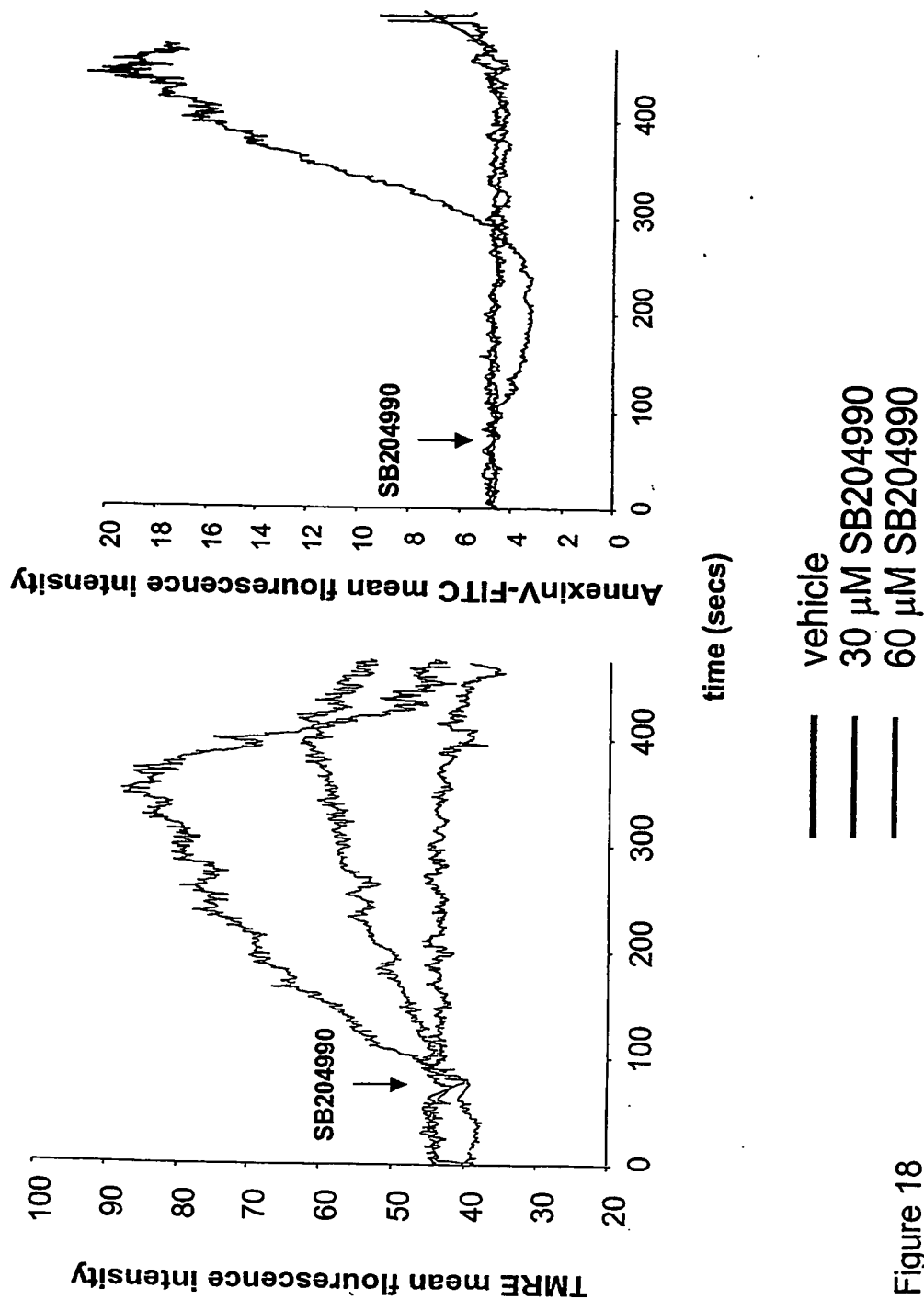


Figure 18